

### **Remarks/Arguments**

Claims 39-47, 49-51 are pending in this application. The rejections to the claims are respectfully traversed.

#### **I. Rejections under 35 U.S.C. §101 and §112, first paragraph**

Claims 39-47, 49-51 remain rejected under 35 U.S.C. §101, for lack of utility, allegedly since the invention is not supported by either a credible, specific and substantial asserted utility or a well established utility (page 2, Item 4 of Office action).

Claims 39-47, 49-51 remain further rejected under 35 U.S.C. §112, first paragraph, allegedly “since the invention is not supported by either a credible, specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention” (page 12, Item 5 of Office action).

Previously, Applicants presented several references to show that MLR is an art-accepted assay for identifying molecules that suppress an immune response in their response filed October 30, 2006. The Examiner acknowledges this on page 3, line 16 of the instant Office action, but maintains that the instant specification does not support utility for the claimed invention, allegedly, because “the specification does not provide any values or data for the proteins tested in the assay. The specification does not provide any statistics for the values measured in the assay.” The Examiner adds that “the specification provides no information at all regarding the results of the assay except that certain proteins tested positive and the statement that ‘any value greater than control indicates a stimulatory effect for the test protein’.”

Once again, Applicants disagree and submit that the Examiner is applying a standard that might be appropriate if the issue at hand were the **regulatory approval of a drug** based on the immunoenhancer activity of PRO335, but is **fully inappropriate for determining if the “utility” standard of the Patent Statute is met**. The FDA, reviewing an application for a new immunoenhancer drug, will indeed ask for actual numerical data, statistical analysis, and other specific information before the drug is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards of market approval. The standards for determining Utility were discussed in detail in the previous response and are hereby incorporated by reference. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with

regard to safety and efficacy of drugs to marketed in the United States. Indeed, in *Nelson v. Bowler*, the Federal Circuit found that the identification of a pharmacological activity of a compound provides an “immediate benefit to the public” and satisfies the utility requirement. This logically applies to the instant utility as well. The identification of a compound as an immunoenhancer should suffice to establish an “immediate benefit to the public” and thus to establish patentable utility.

Applicants add that the MLR assay described in the instant specification is a comparative one (increases of greater than or equal to 180% is preferred), meaning that the utility is based upon a comparison of relative expression levels between a known polypeptide and an unknown PRO molecule. And Applicants expressly assert that the observed difference for PRO335 is significant as discussed in Example 74 of the instant specification. Example 74 says that the standard to be used to determine whether a positive result in the MLR assay is significant, stating that “[p]ositive increases over control in this assay are considered to be positive results, with increases of greater than or equal to 180% being preferred and that PRO335 tested positive in this assay. However, any value greater than control indicates a stimulatory effect for the test protein” (page 203, line 27). By focusing on a requirement for numerical data, or on statistical analysis, the Examiner is placing a higher standard for determining the utility of PRO335. Applicants submit that PRO335 significantly shows enhanced activities in the MLR assay, which renders the claimed invention useful as a stimulator for enhancing immune response.

The Examiner maintains, regarding the Fong Declaration, that it is not persuasive and that “the expert has interest in the outcome of the case since (he) is listed as an inventor and is employed by the assignee.” The Examiner questions the significance of the expert’s conclusions based on alleged lack of use of proper controls.

Applicants respectfully submit that Dr. Fong’s statements are made under oath, and are asserted based on his vast knowledge and experience in the use and interpretation of the MLR assay. Furthermore, assay controls were extensively discussed in previous responses, and is incorporated herein in their entirety. Yet, the Examiner says that proper assay controls were not used, without giving any valid reason for doubting or questioning the assay controls used in the instant invention. Applicants maintain that the assay controls used in the instant invention were appropriate, as discussed in clear detail in the Fong Declaration and throughout prosecution, and

thus, the data for PRO335 in Example 74 (MLR assay) would be considered as meaningful, by one skilled in the art.

Applicants add that references Gubler *et al.* and Peterson *et al.* were submitted, not to show MLR activities of PRO335 (which is novel), but to show that other investigators used similar MLR assays to the one described in the instant specification, to conclude that their molecules stimulate T-cell proliferation and can be useful to enhance immune response. Applicants maintain their position regarding references Gubler *et al.* and Peterson *et al.*

For the reasons given above, Applicants respectfully submit that the results of the MLR assay as shown in Example 74 of the present specification, provide a specific, substantial and credible utility under 35 U.S.C. §101 for the claimed invention.

## **II. Rejection under 35 U.S.C. §112, first paragraph Enablement**

Claims 39-47, 49-51 remain further rejected under 35 U.S.C. §112, first paragraph, allegedly “since the invention is not supported by either a credible, specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention” (page 12, paragraph 2 of Office action).

The Examiner does not accept these arguments and indicates that “the ability of the claimed antibody or PRO335 protein to stimulate or inhibit lymphocyte proliferation in the MLR assay does not provide for what specific conditions, or for which specific diseases the claimed invention would predictably function for a therapeutic suppression of the immune system” (page 12, paragraph 4 of Office action).

Claims 39-43 are directed to antibodies to the polypeptide of SEQ ID NO: 290 where the polypeptide has a specific and useful function (*i.e.* as "immunostimulants" useful for boosting the immune system of an animal. Specific conditions for the use of immunostimulants like PRO335 have been discussed extensively in the response filed October 30, 2006, which are hereby incorporated by reference. For instance, applicants submitted that cytokines like IL-2, etc. and other immunostimulants were well-known, researched and used to stimulate cellular immunity in various cancers (see references cited within Steinman, Thurner and Gubler *et al.*) at the effective filing date. In fact, Steinman *et al.* (Exhibit B) states "...medicine needs therapies that enhance immunity or resistance to infections and tumors" (page 1, column 1, line 7;

emphasis added). In this regard, Applicants respectfully remind the Examiner that the skilled artisan in the field of Immunology and Immunotherapeutics, at the effective filing date of September 17, 1998, would likely be a person with a Ph. D. or M.D. degree, sometimes both, with extensive experience. Thus, one skilled in the art could easily test whether a native variant PRO335 protein was an immunostimulant in the MLR assay (as described in the Example 74 of the specification and in Current Protocols) and evaluate whether PRO335 was useful in the treatment of any cancer, as described in the art (see references cited within Steinman, Thurner and Gubler *et al.*). As the M.P.E.P. states, “[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.”<sup>11</sup> Thus, based on the general knowledge in the art, one skilled in the art, at the effective date of the present application, would have known that any immunostimulant (just like cytokines) are useful for stimulating or boosting the immune system of an animal, which in turn is useful, for example, to improve or increase immune surveillance in diseases like cancer.

Applicants also note that the specification clearly indicates that the claimed polypeptides are useful in the treatment of undesirable immune responses. The use of immunosuppressive molecules in the treatment of such disorders is well known in the art, as indicated by Kahan *et al.*, Picotti *et al.* and Campo *et al.*, made of record by the Examiner, as well as the references and U.S. Patents, discussed and made of record in the IDS filed on October 30, 2006. Thus any further experimentation required for determining, for example, a particular dosage or method for the administration of PRO335 would not be considered undue. MLR was routinely used in the art to identify immunostimulants or immunosuppressors, and additionally, were found to have *in vivo* utility, in the treatment of cancer and other related conditions. The importance of immunostimulants in the treatment of cancer or in enhancing the effectiveness of previously identified treatments for cancer, including tumor-specific antibodies, were well known in the art at the time of filing of the instant application. For instance, costimulation of T-cells inducing tumor regression and an antitumor response, both *in vitro* and *in vivo* was known (for e.g.,

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<sup>11</sup> M.P.E.P. 2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v. A.B. Fortia* 774 F 2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

Steinman *et al.* submitted as Exhibit B with the Response filed October 25, 30, 2004). Thus, one skilled in the art would know that immunostimulating compounds like IL-12 or PRO335 of this invention, could be useful in immunoadjuvant therapies, for the treatment of tumors (cancer) and could be administered either alone or together with other agents to stimulate T-cell proliferation/activation (immune function). These could be done without undue experimentation.

Applicants also note that the Examiner has failed to point out several instances within cited references like the teachings within Basic and Clinical Immunology, Kahan *et al.*, Piccotti *et al.*, Campo *et al.* wherein the authors stated that the MLR is an important method with a good predictive value. For example, Campo *et al.* teach that “the human mixed lymphocyte culture (MLC) is an important method to test donor-recipient compatibility in bone marrow transplantation. It could be shown that cytokine release, especially IFN-gamma, **has a very good predictive value with regard to the transplantation outcome**, as cytokines play a major role in the generation of an alloreactive immune response and for the induction of graft rejection *in vivo*.....Landolfo *et al.* inhibited T-cell reactivity by the addition of anti-IFN-gamma **both in vitro and in vivo**” (see page 18; emphasis added). Finally, Campo *et al.* teaches that “cyclosporin A, FK506, and other substances are used to prevent graft rejection. **In vitro experiments revealed an inhibition of the MLC**” (page 16). Thus the teachings of Campo *et al.* confirm that inhibition of the MLR is observed for known immunoinhibitory molecules, that are in actual clinical use.

Applicants further submit that enablement “is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive.” As the M.P.E.P. states, “[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.” The M.P.E.P. further explains that “If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. §112 is satisfied.”

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With respect to disclosure of the results of *in vitro* assays, the M.P.E.P. states that “**if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate.** Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995).”

Therefore, based on the extensive art, one skilled in the art would know that agonistic immunostimulating antibodies are useful in treating, for instance, neoplastic tumors, or antagonistic antibodies -immunosuppressors, are useful for instance, in treating diseases like autoimmune or graft vs. host disease). Further, given the disclosure in the specification, one skilled in the art would be able to make and use the claimed amino acid sequence of SEQ ID NO: 290, and sequences with at least 80% identity to SEQ ID NO: 290 to stimulate T-cell proliferation/activation (immune function), for example in cancer. Accordingly, one of ordinary skill could make the claimed invention without undue experimentation.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of Claims 39-47 and 49-51 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

### **III. Rejections under 35 U.S.C. §112, first paragraph**

Claims 39-43, 50 and 51 are rejected under 35 U.S.C. §112, first paragraph, allegedly as failing to comply with the written description requirement. The claims allegedly contain subject matter which was not described in the specification, at the time the application was filed, to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Applicants respectfully disagree.

For the reasons discussed in their response of October 30, 2006, Applicants maintain that the present application meets the standards required for fulfilling the 35 U.S.C. §112, first paragraph- written description requirement. The Examiner adds “(u)sing the approximation formula, the number of possible amino acid sequences and nucleotide sequences that are at least

e.g. 80% identical to the reference amino acid sequences or nucleotide sequences would be much larger than  $6 \times 10^{23}$  and  $1.6 \times 10^{56}$ , respectively.”

The Examiner seems to miss the point. Applicants claim only those nucleic acid sequences that encode proteins which meet both recitations of the claims **structural and functional**. The specification describes methods for the determination of percent identity between two amino acid sequences (See page 67, line 34, to page 69, line 24). In fact, the specification teaches specific parameters to be associated with the term “percent identity” as applied to the present invention. **The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 112, line 37 to page 115, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 114).** Accordingly, one skilled in the art would know that every amino acid residue need not be changed in order to obtain 80-99% variants. Using Table 6 of the specification, one skilled in the art would change preferred substitutions only, in order to get meaningful and functional proteins. That greatly reduces the number of possible polypeptides. Once such an amino acid sequence is identified, the specification sets forth methods for making the nucleic acid sequences (see page 117, line 10, to page 121, line 30) and methods of preparing the PRO polypeptides from the nucleic acids.

In view of the above, Applicants respectfully request reconsideration and reversal of the written description rejection of Claims 39-43, 50 and 51 under 35 U.S.C. §112, first paragraph.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any additional fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C46). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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